

REMARKS

Claims 1-10 and 12-52 are currently pending in the present application.

RESPONSE TO OBJECTIONS

As requested by the Examiner, Applicant has amended the specification to recite the SEQ ID NOs of the peptides recited at page 9, lines 2-3. Accordingly, Applicant submits that this objection should be withdrawn.

Claim 11 was objected to since the text was presented in the claims listing even though claim 11 had been cancelled. The complete listing of claims presented with the present response does not include the text of claim 11. Accordingly, Applicant submits that this objection should be withdrawn.

At page 3, ¶ 2 of the Office Action, the Examiner objects to claims 1, 25 and 27 because of the recitation of “and/or” at the end of the third to last line of part (a) of each claim. Applicant has amended claims 1, 25 and 27 to only recite “or.” Accordingly, Applicant submits that this objection should be withdrawn.

At page 3, ¶ 3 of the Office Action, the Examiner objects to the current ordering of claims, and invites Applicant to suggest a final ordering of claims to appear in a patent. As invited, Applicant suggests the following order of claims in the issued patent: Claims 1-2, 45, 3-10, 46-48, 12, 22, 13-17, 49, 18-21, 23-27, 39, 28, 50, 29-30, 35, 52, 31-34, 36-38, 40-44, 51.

Written Description Rejections

Claims 29-35, 42, 43, and 45-52 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement on various bases. Each basis is discussed in turn.

Claims 27-52, 29-35, 42, 43, and 45-52 stand rejected under 35 U.S.C. 112, first paragraph, based on the Examiner’s assertion that the specification lacks support for the limitation in these claims reciting “at least 27%” of the amino acids in the peptide are histidine. According to the Examiner, a working example describing a peptide 29 amino acids long which has a histidine content of 27.5862068965...% is insufficient to support the genus of peptides having at least about 27% histidine (regardless of peptide size). Rephrasing the Examiner’s contention in the context of a written description analysis, the Examiner appears to be asserting that one skilled in the art would not recognize Applicant as having been in possession of the

genus of transport polymers comprising a peptide having at least 27% histidine content based on a single example (SEQ ID NO: 7). Applicant respectfully disagrees. In particular, the Examiner's finding is premised on a skilled artisan reading Applicant's specification as teaching that the size of SEQ ID NO: 7 (i.e., 29 amino acids) was an essential factor in the ability of a peptide corresponding to SEQ ID NO: 7 to enhance transfection efficiency. Stated another way, the Examiner's finding is premised on a skilled artisan reading Applicant's specification as teaching that peptides of different sizes have different minimum histidine contents before they are capable of enhancing delivery of pharmaceutical agents. While Applicant agrees that the specification would lack support if a skilled artisan understood the disclosure to suggest that peptides of different sizes have different minimum histidine contents before they are capable of enhancing delivery of pharmaceutical agents, as elaborated below, the specification clearly teaches the opposite and the Examiner has not presented evidence to the contrary.

Applicant directs the Examiner's attention to page 12 of the current specification. The second paragraph on page 12 describes the size of the polypeptides useful as transport polymers. As stated at line 5, it is preferred that the polypeptide have at least 10 amino acids. The third paragraph on page 12 describes the histidine content of the polypeptides useful as transport polymers. As indicated at line 13, it is preferred that the transport polymer have at least about 5% histidine, more preferably at least about 10%, still more preferably at least about 40%. Importantly, neither paragraph indicates that peptides of different sizes have different minimum histidine content requirements in order to enhance pharmaceutical agent delivery.

Applicant further directs the Examiner to page 26, lines 1-9 (§ 6.4.2), which reports a working example demonstrating the effect of varying the length of the histidine copolymer on transfection efficiency. The three histidine copolymers tested, SEQ ID NOs: 1, 3 and 4 had similar histidine contents (38.5%, 42.1% and 41.4% respectively). One skilled in the art would clearly conclude from the results reported in Figure 3 of the specification, that the size of the histidine copolymer has an effect on delivery of pharmaceutical agents independent of its histidine content. Stated another way, one skilled in the art would clearly conclude from these results that use of a peptide having at least 13 amino acids and a histidine content of at least about 40% as a transport polymer will enhance delivery of pharmaceutical agents.

Applicants cited SEQ ID NO: 7 as support for a limitation reciting that the histidine copolymer have at least 27% histidine content. Applicant directs the Examiner's attention to

page 29, lines 7-15 (§ 6.4.10), which reports a working example which indicates that a peptide corresponding to SEQ ID NO: 7 was capable of enhancing transfection efficiency.

Returning back to the rejection, the Examiner contends that SEQ ID NO: 7 is not sufficiently representative of the genus of peptides having at least about 27% histidine content because it is 29 amino acids long and a skilled artisan would have considered the size of the peptide important. In view of the results reported in § 6.4.2 of the specification (discussed above); however, the skilled artisan would clearly conclude that other peptides having a different length but also having a histidine content of at least about 27% would also enhance transfection efficiency. Further, one skilled in the art would clearly consider the genus of peptides having at least about 27% histidine content as part of Applicant's invention in view of the teaching at page 12, ¶ 3 (discussed above) that the histidine copolymers of the invention have at least about 5% histidine, more preferably at least about 10%.

When the claims at issue were initially amended to recite "at least about 27%", the Applicant cited *In re Wertheim* as support for the amendment. See MPEP 2163.05 III. Range Limitations (citing *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976)). The facts in *In re Wertheim* are remarkably similar to the present facts, and thus may be helpful for the Examiner to consider. Claim 2 of Wertheim's application claimed a process for minimizing loss of volatiles during freeze-drying of coffee extract which comprised: "obtaining coffee extract, concentrating said extract to a higher solids level of between 35% and 60%, foaming said concentrated extract ..." The issue in *Wertheim* was whether a Swiss application to which priority was sought provided written description support for the "between 35% and 60%" limitation. The Swiss application disclosed concentrating an extract "until a concentration of 25 to 60% solid matter is reached," as well as two examples wherein extract was concentrated to have solid contents of 36% or 50%. The PTO took the position that the specification did not support the claim limitation "between 35% and 60%." The Court of Customs and Patent Appeals disagreed, stating:

[Claim 2] clearly claim[s] a range *within* the described broad range of 25% to 60% solids; the question is whether, *on the facts*, the PTO has presented sufficient reason to doubt that the broader described range also describes the somewhat narrower claimed range. We note that there is no evidence, and the PTO does not contend otherwise, that there is in fact any distinction, in terms of operability of [applicants'] process or of the achieving of any desired result,

between the claimed lower limit of solids content and that disclosed in the Swiss application.

In the context of *this* invention, in light of the description of the invention as employing solids contents within the range of 25%-60% along with specific embodiments of 36% and 50%, we are of the opinion that, as a factual matter, persons skilled in the art would consider processes employing a 35-60% solids content range to be part of [applicants'] invention and would be led by the Swiss disclosure so to conclude. The PTO has done nothing more than to argue lack of literal support, which is not enough. If lack of literal support alone were enough to support a rejection under §112, then the statement of *In re Lukach* ... that "the invention claimed does not have to be described in *ipsis verbis* in order to satisfy the description requirement of §112," is empty verbiage. The burden of showing that the claimed invention is not described in the specification rests on the PTO in the first instance, and it is up to the PTO to give reasons why a description not in *ipsis verbis* is insufficient.

191 USPQ at 98 (citations omitted).

Similar to the applicant in *In re Wertheim*, Applicant's claims recite a transport polymer comprising a peptide having a narrower range of histidine content (i.e., at least 27%) than the broader range of peptides disclosed in the specification (i.e., "at least about 5% histidine, more preferably at least about 10%"), as well as a narrower range of peptide size (if linear, "at least 13 amino acids") than the broader range of peptide size disclosed in the specification (preferably at least about 10 amino acids). Like in *In re Wertheim*, the Examiner presents no evidence and does not contend that there is in fact any distinction, in terms of operability of the peptides to enhance pharmaceutical agent delivery, between the claimed lower limit of histidine content and size and that disclosed in Applicant's specification. Furthermore, Applicant's specification contains a disclosure of a working embodiment wherein a peptide has 13 amino acids, a working embodiment wherein a peptide has a histidine content of 27.586...%, and an example demonstrating that peptide size and histidine content are independent variables as regards the operability of a peptide to enhance pharmaceutical agent delivery. Accordingly, it follows that persons skilled in the art would consider transport polymers comprising a peptide having at least about 27% histidine content as part of Applicant's invention and would be led by Applicant's specification to so conclude. The fact that the specification does not explicitly describe the genus of peptides having at least about 27% histidine content is therefore not relevant. Moreover, Applicant does describe an embodiment having 27.586...% histidine content; and the difference between 27% (as claimed) and 27.586...% (as exemplified in SEQ ID NO: 7) is

smaller than the difference held by the court in *In re Wertheim* to be supported (35% in a claim in view of a specific embodiment of 36%).

In view of the above argument, Applicant respectfully requests withdraw of the 35 U.S.C. 112, first paragraph, rejection that the claims lack written description support for the limitation “at least about 27%.”

Claims 29 and 42, and claims depending to these claims, further stand rejected under 35 U.S.C. 112, first paragraph, based on the Examiner’s assertion that the specification lacks support for the limitation in these claims reciting “at least about 33% of said amino acid residues of said peptide are selected from the group consisting of non-histidine residues which carry a positive charge at physiological pH.” The Examiner further asserts that the combination of this limitation and the “at least about 27%” limitation also lacks support. According to the Examiner, SEQ ID NO: 15 does not provide adequate support, and Applicant has failed to identify any peptide that combines both of the recited limitations or any other teaching that would have directed one of skill in the art to take one characteristic of several characteristics of two different peptides and combine them as the basis for a generic invention. Applicant’s have amended claims 29 and 42 to now recite that “at least about 40% of said amino acid residues of said peptide are selected from the group consisting of non-histidine residues which carry a positive charge at physiological pH.” For the reasons noted below, this limitation alone, and in combination the “at least about 27%” limitation finds support in the original specification.

Claim 29 recites a pharmaceutical agent delivery composition, wherein the pharmaceutical agent comprises nucleic acid. Similarly, claim 42 recites a method for delivering a pharmaceutical agent to the interior of a cell, wherein the pharmaceutical agent comprises nucleic acid. In the “Background and Prior Art” section of Applicant’s specification, in particular, at page 2, lines 20-23, the specification teaches

The addition of poly-L-lysine or protamine to cationic liposome carriers is known to enhance the transfection efficiency of liposomes (9,14-17). These highly basic polymers/proteins effectively condense the plasmid DNA, while liposomes neutralize the remainder of the negative charge of the DNA and provide a scaffold for the polymer:DNA complex.

It was thus well known in the art at the time Applicant’s application was filed that for a peptide to non-covalently associate with DNA (which has an overall negative charge), the peptide must

comprise positively charged amino acids. Regarding the transport polymer component of the pharmaceutical delivery composition of Applicant's invention, at page 12, l. 31 – page 13, line 12, Applicant's specification teaches that:

The non-histidine amino acid(s) may all be the same amino acid residue or they may be different amino acid residues. Where the pharmaceutical agent has an overall negative charge (for example, nucleic acid) the non-histidine amino acid(s) are preferably selected from the group consisting of amino acids with a side-group that carries a positive charge at physiological pH (for example, lysine and arginine). More preferably, the non-histidine amino acid(s) comprise lysine residues. In one aspect of the invention, the non-histidine amino acid(s) are all lysine.

The non-histidine amino acid(s) are also suitably selected from the group consisting of amino acids with a side-group that carries a negative charge at physiological pH (for example, aspartic acid and glutamic acid) as well as amino acids that are neutral at physiological pH (for example, glycine and serine).

Preferably, non-histidine amino acid(s) are selected so as to tailor the transport polymer to the particular pharmaceutical agent and the intended method of association. Thus, where the pharmaceutical agent is a nucleic acid (overall negative charge) and non-covalent association with the transport polymer is desired, the non-histidine amino acid(s) are preferably selected from the group consisting of amino acids with a side-group that carries a positive charge at physiological pH.

A skilled artisan reading the above cited passages in the specification would appreciate that if the pharmaceutical agent is a nucleic acid (overall negative charge) and non-covalent association with the transport polymer is desired, the non-histidine amino acid(s) *are preferably selected* from the group consisting of amino acids with a side-group that carries a positive charge at physiological pH (hereafter, referred to as “cationic amino acids”).

Claims 11 and 22 as originally filed recited a limitation “wherein at least 10% of the non-histidine amino acid residues of said peptide carry a positive charge at physiological pH.” Accordingly, one skilled in the art would recognize that the percentage of non-histidine amino acids which are cationic amino acids is a characteristic of the peptides.

One skilled in the art would understand the passage at page 12, l. 31 – page 13, line 12, in combination with original claims 11 and 22 as an explicit indication by Applicant that not all non-histidine amino acids need to be cationic amino acids in order for a histidine copolymer to non-covalently associate with a nucleic acid. This raises two questions: first, does the histidine component play a role in non-covalent association with nucleic acid; and second, if it doesn't,

what percentage of the non-histidines need to be cationic amino acids in order for a peptide to still non-covalently associate with nucleic acid.

One skilled in the art would find the answer to the first question in Applicant's specification in the results of the elegantly designed experiments described at page 7, lines 13-18 (description of Figures 8 and 9) and page 27, lines 18-30 (§ 6.4.6). Here, Applicant describes an experiment which demonstrates what role histidine and lysine play in augmenting the transfection efficiency of nucleic acid. Figure 8 reports the results of the ability of three different 19-mers: one comprising histidine and lysine (SEQ ID NO: 3); one comprising lysine and serine (SEQ ID NO: 10); and one comprising serine and histidine (SEQ ID NO: 11). The results show that only the 19-mer comprising histidine and lysine showed a statistically significant increase over the control (i.e., no transport polymer). One skilled in the art would conclude two important points from these results. First, since the only difference between the H-K (19-mer) and the S-K (19-mer) was the substitution of histidines with serines, it is clear that the histidine component is critical to enhancing transfection efficiency and that the lysine component plays no direct role in enhancing transfection efficiency. Second, since the only difference between the H-K (19-mer) and the H-S (19-mer) was the substitution of lysines with serines, it is clear that histidine amino acids do not play a role in binding and condensing DNA (i.e., non-covalent association with nucleic acid). Figure 19 shows the results comparing the ability of an H-K (19-mer) and an H-R (19-mer) to enhance transfection efficiency. Both 19-mers enhanced transfection efficiency. Since the only difference between the H-K (19-mer) and the H-R (19-mer) was the substitution of lysines with arginines (i.e., another cationic amino acid), one skilled in the art would clearly conclude that the cationic component of a transport polymer peptide can be any amino acid with a side-group that carries a positive charge at physiological pH. Furthermore, one skilled in the art would also conclude that the characteristic of the peptides of the invention which permits enhanced transfection efficiency (i.e., the peptides histidine content) is distinct from the characteristic of the peptides of the invention which permits any particular peptide to non-covalently associate with nucleic acid (i.e., the peptides cationic amino acid content).

Regarding the second question, (that is, what percentage of the non-histidine amino acids need to be cationic in order for a peptide to still non-covalently associate with nucleic acid?), Applicant refers the Examiner's attention to page 29, lines 16-23 of the specification (and Figure 14), which reports that two peptide 20-mers, (SEQ ID NO: 6) and (SEQ ID NO: 5), were capable

of enhancing transfection efficiency. Both of these peptides comprise 8 lysines (that is, 40% amino acids with a side-group that carries a positive charge at physiological pH). Thus one skilled in the art would clearly understand Applicant as teaching that a peptide having at least about 40% cationic amino acids would be sufficient to permit non-covalent association with nucleic acid.

For the reasons noted above, a skilled artisan would clearly recognize that Applicant was in possession of the genus of peptides having at least about 27% histidine content, and in possession of the genus of peptides (capable of non-covalently associating with nucleic acid) having at least about 40% cationic amino acids. As further noted above, one skilled in the art would also understand Applicant's specification to teach that the characteristic of the peptides of the invention which permits enhanced transfection efficiency (i.e., the peptides histidine content) is distinct from the characteristic of the peptides of the invention which permits any particular peptide to non-covalently associate with nucleic acid (i.e., the peptides cationic amino acid content). Given the independence of these peptide characteristics, one skilled in the art would clearly be led to select peptides having the particular characteristics recited in claims 29 and 42. In particular, both of these claims recite a pharmaceutical agent delivery composition, wherein the pharmaceutical agent comprises nucleic acid. In view of the need for the peptide to have an overall positive charge in order to non-covalently associate with the nucleic acid, Applicant's specification clearly would lead a skilled artisan to the genus of peptides having 27% histidine content and at least about 40% cationic amino acids since this genus merely represents the intersection of the two independent genera of peptides taught in Applicant's specification.

The Examiner finally contends that the claims rejected under 35 U.S.C. 112, first paragraph, lack written description support as to branched peptides having the specific histidine and non-histidine content limitations. Applicants respectfully traverse this rejection. As regards peptides having 27%, applicants note that the specification makes no distinction between linear and branched peptides as regards histidine content. See in particular, page 12, lines 5-25. Importantly, nothing in the specification suggests that peptides of different sizes (linear or branched) have different minimum histidine content requirements in order to enhance pharmaceutical agent delivery. Accordingly, in the absence of evidence to the contrary, the "at least about 27%" histidine content limitation is clearly supported as to both linear and branched

peptides for the reasons noted above. Additionally, as noted above, claims 29 and 42 have been amended to recite at least about 40% amino acids with a side-group that carries a positive charge at physiological pH. Applicant directs the Examiner's attention to pages 30-31 (§ 6.4.13), which reports results from experiments indicating that three branched polymers, HH-K4b, HH-K3b, and HH-K2b were capable of enhancing transfection efficiency. The formula for these three peptides (see page 23, lines 15-17) indicates that they consist of a total of 83, 62 and 41 amino acids respectively. The formula further indicates that they have 35, 26 and 17 lysine residues. It is noted, however, that the side-chains of respectively 3, 2 and 1 lysines are involved in forming the branches (via peptide bonds). Accordingly, HH-K4b, HH-K3b, and HH-K2b respectively contain 38.6% (i.e., $100\% \times 32/83$), 38.7% (i.e., $100\% \times 24/62$) and 39.0% (i.e., $100\% \times 16/41$) with a side-group that carries a positive charge at physiological pH. Thus, Applicant's data clearly would convey that a branched peptide comprising at least about 40% amino acids with a side-group that carries a positive charge at physiological pH would be operable and thus indicates Applicant's possession of this genus. Finally, as noted above, the specification clearly teaches that the histidine content and cationic amino acid content of peptides are independent characteristics. In the context of the particular claims, however, which specifically are directed to delivery of nucleic acid, one of skill in the art would have recognized Applicant's as being in possession of the genus of peptides (linear or branched) having at least about 27% histidines and at least about 40% amino acids with a side-group that carries a positive charge at physiological pH.

DOUBLE-PATENTING REJECTION

While not necessarily agreeing with this rejection, applicant submits herewith a terminal disclaimer in compliance with 37 CFR 1.321(c) along with the \$65 fee under 37 CFR 1.20(d).

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance; however, if the Examiner disagrees, the applicants respectfully request that the Examiner telephone the undersigned at (302) 888-6210.

Applicant believes that no other fees in addition to the \$65 fee under 37 CFR 1.20(d) are due in connection with this response. If there are any other fees due in connection with the filing

of this response, including any fees required for an extension of time under 37 CFR 1.136, such an extension is requested and the Commissioner is authorized to charge any debit or credit any overpayment to Deposit Account No. 03-2775, under Order No. 05627-00005-USA from which the undersigned is authorized to draw.

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Respectfully submitted,

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